CASE OP/V-30341B/D1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
KIS ET AL.
APPLICATION NO: 10/016,361
FILED: DECEMBER 10, 2001
FOR: AUTOCLAVABLE PHARMACEUTICAL COMPOSITIONS CONTAINING A CHELATING AGENT

Art Unit: 1616
Examiner: R. Joynes

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Troy A. Reaves, residing at 6625 Ridgefield Drive in Alpharetta, Georgia (30005) declare as follows:

1. I was the Director of Clinical Affairs at Ciba Vision Corporation from August 1991 to November 1997. My undergraduate degree (B.S., 1969) is in Biology and my graduate degrees are in Biology (M.S., 1971, cardiovascular physiology) and in Physiology & Biophysics (Ph.D., 1976, neuroscience). As an Assistant Professor of Neurology/Neurobiology Program at the University of North Carolina in Chapel Hill, I was involved in basic and applied research of the neuro-endocrine system and in neurobiology which resulted in over 4 dozen peer-reviewed publications. Over the last nineteen years, I have held various positions of responsibility in the ophthalmic pharmaceutical industry exclusively in the area of clinical research. During this time, I have directed clinical research efforts on several investigational new drug candidates for the treatment of ocular allergic conditions. Since November 1997, I have directed the Novartis clinical programs (Clinical Program Leader) in treating exudative age-related macular degeneration with photodynamic therapy using verteporfin. Currently, I am a Senior Director with Novartis and my resume includes more than 2 dozen publications in ophthalmology. My CV is attached as Exhibit A.

2. I have read and understood the present application.

3. I have read and understood the Office Action mailed on March 26, 2003 in which the Examiner rejected claims 1-14 under 35 U.S.C. §103(a) as being unpatentable over the translation of JP62277323.

4. While I was the Director of Clinical Affairs at Ciba Vision Corporation, I supervised Phase II Studies in 1997 which pertained to the clinical evaluation of ketotifen fumarate (KE) ophthalmic solutions in relieving ocular itching, a hallmark symptom of allergic conjunctivitis. The experimental methods and results for these studies are described below.

Phase II Studies – A Dose-Response Evaluation of KE Ophthalmic Solution in Varying Concentrations Against Placebo (PL) Control in the Allergen Challenge Model

Methods

A primary objective of the study was to compare the efficacy, onset and duration of action, and to determine the optimal concentration of KE ophthalmic solution versus PL in the relief of ocular itching induced by the allergen challenge model also known as the conjunctival provocation model (CPT). The model as described, e.g., by Abelson and Spitalny, *Am. J. Ophthalmol.*, Vol. 125, No. 6, pp. 797-804 (1998) (Exhibit B) is accepted by the USFDA as an appropriate surrogate to wild-type allergic conjunctivitis seen in humans. The USFDA has approved several antihistamines for treating allergic conjunctivitis after reviewing data from this model (Livostin®, levocabastine HCl 0.05%, NDA 20-219, November 1993; Patanol®, olopatadine HCl 0.1%, NDA 20-688, December 1996; and Emadine®, emedastine difumarate 0.05%, NDA 20-706, December 1997). The model provides reproducible data in a standardized experimental setting avoiding in the process variability in signs and symptoms of ocular allergy.

The following four concentrations of KE ophthalmic solution were evaluated for efficacy in relieving ocular itching:

- KE 0.025% ophthalmic solution (equivalent to ketotifen fumarate 0.0345% weight/volume)
- KE 0.05% ophthalmic solution (equivalent to ketotifen fumarate 0.069% weight/volume)
- KE 0.1% ophthalmic solution (equivalent to ketotifen fumarate 0.138% weight/volume)
- KE 0.15% ophthalmic solution (equivalent to ketotifen fumarate 0.207% weight/volume)

Each of the four KE solutions was prepared as an ophthalmic formulation containing the following ingredients: glycerol (21.25 mg/mL equivalent to 2.125% with an osmolarity in the range of 210-290 milliosmoles), benzalkonium chloride (0.01%), purified water, hydrochloric acid

and/or sodium hydroxide (to adjust the pH). Olopatadine Hydrochloride (OL) 0.1% ophthalmic solution (Alcon Laboratories, Inc.) was utilized as an active control. All treatments were topical ophthalmic eye drops.

To receive study treatment subjects must have had: 1) an allergic history to animal dander and/or seasonal airborne allergens such as ragweed, mountain cedar, etc. which was assessed along with other inclusion/exclusion criteria at Visit 1 (screening of subjects); and 2) a successful allergen challenge reaction, inducing at least 2+ itching and 2+ conjunctival redness in both eyes within 10 minutes at Visits 1 and 2 (confirmatory challenge for enrollment purposes).

Selected subjects (129) were randomized to receive one of the four different concentrations of KE ophthalmic solution or OL 0.1% solution in one eye and PL in the other eye beginning at Visit 3. At Visit 3 (the onset-of-action challenge), subjects received assigned treatment to each eye 15 minutes before receiving the allergen challenge which consisted of ragweed pollen, tree pollen or cat dander. Efficacy was determined from the subject's rating of itching at approximately 3, 7, 10, 15 and 20 minutes after allergen challenge. Subjects then underwent a 2-week washout period between Visits 3 and 4..

At Visit 4 (the first duration-of-action challenge), subjects received treatment approximately 8 hours before allergen challenge. Effectiveness was measured for subjective itching at 3, 7, 10, 15 and 20 minutes after allergen challenge. Subjects then underwent another 2-week washout period between Visits 4 and 5. At Visit 5 (the second duration-of-action challenge), subjects received treatment approximately 12 hours prior to allergen challenge. Efficacy measurements were made at the same intervals used at Visits 3 and 4.

The intensity of ocular itching was evaluated on a 5-point scale (0-4), where 0 represents no itching. Increments of 0.5 were allowed so that scores of 0.5, 1.5, 2.5 and 3.5 could also be used by the subject. Ocular itching scores between 0 and 1 represent extremely mild itching; scores between 1 and 2 represent mild itching; scores between 2 and 3 represent moderate itching; and scores between 3 and 4 represent severe or extremely severe itching.

For ocular itching, the primary efficacy variable, efficacy was established by achieving a mean between-treatment difference of approximately 1 unit at 4 of 5 time points. This difference was calculated as the mean of the inter-ocular differences within each subject (placebo-treated eye minus active-treated eye) for each treatment group at each visit.

Results

The time course of the unadjusted between-treatment differences in ocular itching at Visits 3, 4, and 5 is shown below in Figures 1, 2 and 3, respectively. The raw data for the time course of the unadjusted between-treatment differences in ocular itching at Visits 2, 3, 4 and 5 are summarized in the Table below.

Figure 1. Itching Differences From Placebo (Visit 3- Onset-of-Action Challenge)

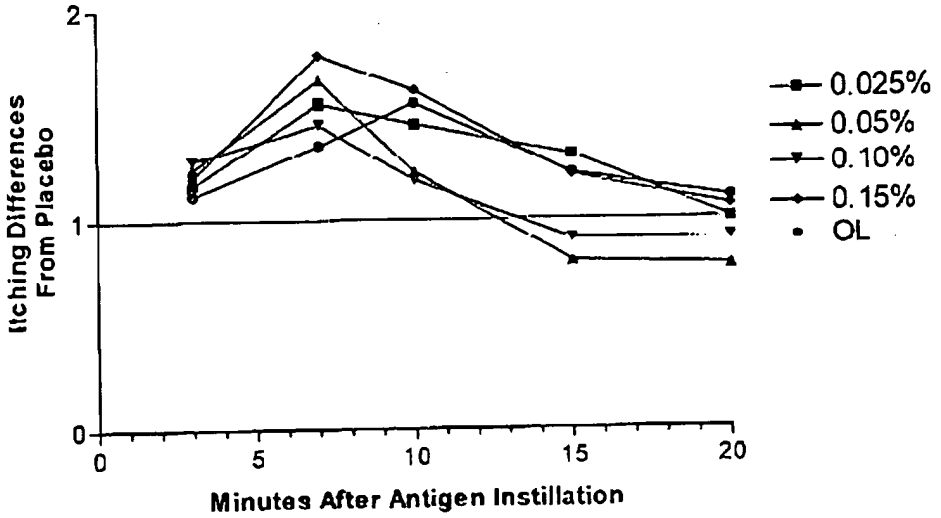

Figure 2. Itching Differences From Placebo (Visit 4- 8-Hour Duration-of-Action Challenge)

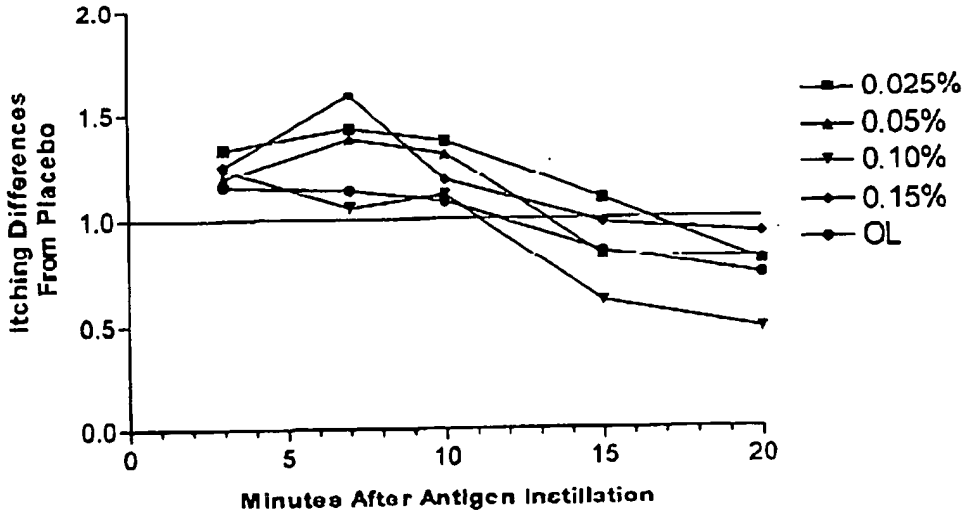

Figure 3. Itching Differences From Placebo (Visit 5- 12-Hour Duration-of-Action Challenge)

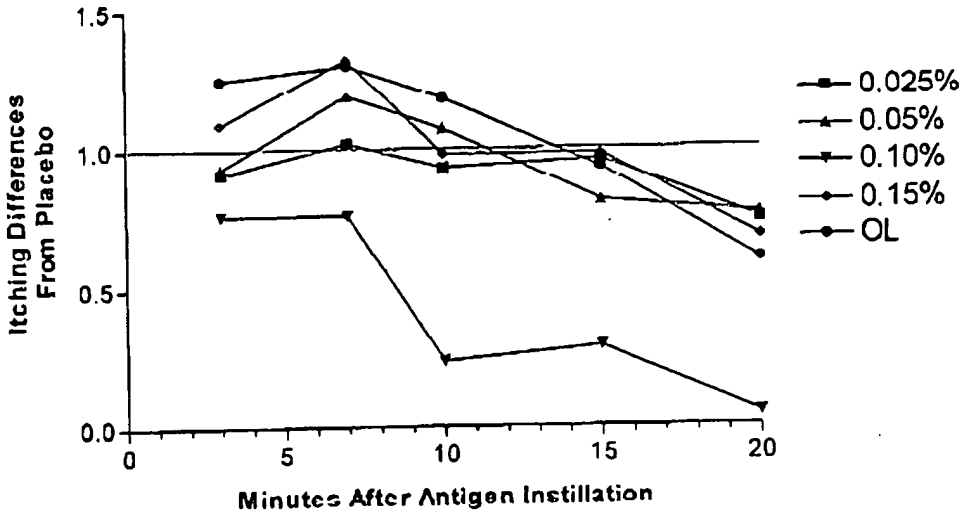

Table. The Effect of Ketotifen Fumarate and Olopatadine Hydrochloride on Itching in the CPT Model

Assessment Time Post Challenge	Treatment	Mean Unadjusted Difference Between Eyes			
			Time of Challenge Post-Treatment		
		Baseline+ (Visit 2)	15 minutes (Visit 3)	8 hours (Visit 4)	12 hours (Visit 5)
3 minutes	KE 0.025%	0.00	1.17	1.33	0.91
	KE 0.05%	0.02	1.25	1.19	0.93
	KE 0.10%	0.02	1.29	1.23	0.76
	KE 0.15%	-0.06	1.21	1.25	1.09
	OL 0.10%	0.08	1.12	1.15	1.25
7 minutes	KE 0.025%	0.06	1.56	1.43	1.02
	KE 0.05%	0.08	1.67	1.38	1.19
	KE 0.10%	-0.06	1.46	1.05	0.76
	KE 0.15%	0.04	1.79	1.59	1.32
	OL 0.10%	-0.06	1.36	1.13	1.30
10 minutes	KE 0.025%	-0.06	1.46	1.37	0.93
	KE 0.05%	0.10	1.23	1.31	1.07
	KE 0.10%	0.00	1.19	1.11	0.24*
	KE 0.15%	0.12	1.62	1.18	0.98
	OL 0.10%	0.10	1.56	1.08	1.18
15 minutes	KE 0.025%	0.10	1.31	1.09	0.96
	KE 0.05%	0.06	0.79	0.83	0.81
	KE 0.10%	0.06	0.90	0.61	0.29*
	KE 0.15%	0.08	1.21	0.98	0.98
	OL 0.10%	-0.02	1.22	0.85	0.93
20 minutes	KE 0.025%	0.02	1.00	0.80	0.74
	KE 0.05%	0.13	0.77	0.81	0.76
	KE 0.10%	-0.04	0.90	0.48	0.05*
	KE 0.15%	0.08	1.06	0.93	0.68
	OL 0.10%	0.02	1.10	0.73	0.60

*P-value >0.050; based on a paired t-test.
+Confirmatory allergen challenge for meeting enrollment into the study.

At Visit 2 (confirmatory allergen challenge for enrollment purposes) within 3 minutes after instillation of the sensitizing antigen, the study subjects reported moderate itching in the challenged eye. Itching peaked within 7 minutes of allergen challenge and became milder 20 minutes after allergen challenge. At Visits 3, 4 and 5 (see Figures 1, 2 and 3, respectively, and Table), itching was present at 3 minutes after instillation of the allergen. Itching peaked at the 7-

minute timepoint, remained intense at the 10-minute timepoint and notably decreased 15 and 20 minutes after the allergen was instilled.

At Visits 3 and 4 (see Figures 1 and 2, respectively, and Table) at all post-challenge time points, all four concentrations of KE solution were statistically superior to PL in preventing the onset of ocular itching. At Visit 5 (see Figure 3 and Table), all four concentrations of KE solution were statistically superior to PL in preventing the onset of ocular itching at all post-treatment time points, with the exception of the KE 0.1% concentration at 10, 15 and 20 minutes. In addition, no apparent ordered-dose relationship was observed in Visits 3, 4 and 5 (see Figures 1, 2 and 3, respectively, and Table) at any time point when determining the efficacy of KE ophthalmic solutions (0.025%, 0.05%,0.1% and 0.15%) versus PL by the prevention of ocular itching induced in subjects by the allergen challenge model. Accordingly, the 0.025% KE solution was found to have comparable efficacy in preventing ocular itching to the three other concentrations of KE solution tested. All four concentrations of KE solution were also found to have a comparable prolonged duration of action and prevented the development of the ocular itching response in eyes challenged with sensitizing antigens over a 12-hour period. Accordingly, the 0.025% KE solution was found to have a comparable prolonged duration of action to the three other concentrations of KE solution. The findings of 1) a lack of an ordered-dose relationship among the four KE concentrations tested indicating that the 0.025% KE solution was as efficacious as the other concentrations of KE solution; and 2) a prolonged duration of action observed for the 0.025% KE solution that was comparable to the other three concentrations of KE solution, were surprising and unexpected. These findings were surprising and unexpected since drug agents for the treatment of ocular allergic conditions generally show an ordered-dose relationship up to the drug concentration that may cause ocular irritation or toxicity. The surprising and unexpected nature of these findings are further supported by the findings in Fujita et al., J. Clin. Ther. Med., Vol. 5, No. 4, pp. 719-721 (1989) (Exhibit C), which demonstrated that in treating allergic conjunctivitis, 0.025% KE ophthalmic solution was found to be significantly less efficacious than the 0.05% KE ophthalmic solution.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true, and further that these statements were made with the knowledge that willfully false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and that willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

23 SEPT. 2003
Date

Dr. Troy A. Reaves